IN THE SPECIFICATION:

Please amend the second full paragraph appearing on page 2 as follows:

Accordingly, it is an object of the present invention to provide a composition comprising a sustained-release drug formulation for sustained delivery of isovaleramide, isovaleric acid, and related compounds for the treatment of various pathologies by effecting a modulation of CNS activity without producing excessive sedation, muscle weakness, fatigue, teratogenicity or hepatotoxicity. ~~Such~~ Such a composition is useful for treatment of convulsions, spasticity, affective mood disorder, neuropathic pain syndrome, migraine and other headache pathologies, restlessness syndrome, movement disorder, substance abuse/craving, cerebral trauma and anxiety-related disorders such as restlessness, nervousness, inability to concentrate, over-aggressiveness, irritability, and insomnia as well as symptoms of smoking cessation, treatment of alcoholism and other substance abuse, premenstrual syndrome, menstrual discomfort, and hyperexcitability in children.

Please amend the paragraph bridging pages 2 and 3 as follows:

In accomplishing these and other objectives, there has been provided, according to one aspect of the present invention, a pharmaceutical composition comprising a sustained-release formulation of isovaleric acid, isovaleramide and related compounds. Upon oral administration, the sustained-release formulation releases the active compound over a period of at least 8 to 12 hours (h). With such a formulation, only two administrations ~~of~~ of the drug need to be given each day.

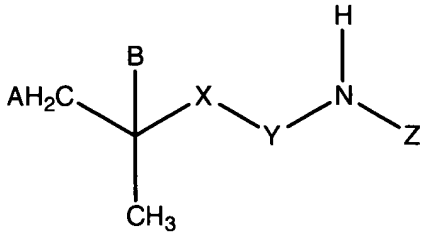
Please amend the fourth full paragraph appearing on page 4 as follows:

Figure 2 portrays a 24-hour dissolution profile of film-coated sustained-release tablets containing 400 mg of isovaleramide (Formulation II, Example 2.1). Dissolution is performed in ~~two stage~~ two-stage media essentially as described in Example 2.1 using simulated gastric fluid without enzymes (SGF) followed by simulated intestinal fluid without enzymes (SIF). Dissolution in SGF and SIF alone also is analyzed. Percent of drug released as determined by HPLC (% label claim) is plotted on the Y axis versus time (hours) on the X axis. At 16 hours, over 75% of the drug is

over 75% of the drug is released under the ~~two-stage~~ two-stage media analysis. Drug release efficiency is greater in SIF as compared to SGF as shown by the individual dissolution profiles.

Please amend the paragraph bridging pages 6 and 7 as follows:

Active compounds also include compounds structurally ~~similarity~~ similar to isovaleramide and ~~which~~ that share similar pharmacological activities. These compounds generally share the common structure:



Where A = H, CH_3, or OH,

B = H, OH, or CH_3,

X = CH_2, $CHCH_3$, $C(CH_3)_2$, -O-, CH(OH), or -CH_2O-,

Y = -CO-, or –SO_2-, and

Z = H, CH_2CO_2H, or CH_2CONH_2,

Please amend the first full paragraph appearing on page 9 as follows:

When the compounds contain one or more asymmetric centers, the individual enantiomers may be prepared from optically active starting materials, or separated by traditional methods of resolution, such as fractional crystallization of salts with chiral amines, or by preparation of amides with chiral amides, chromatographic separation, and hydrolysis of the amides. Alternatively, the amides can be prepared by ~~well known~~ well-known methods of asymmetric synthesis, such as alkylation of an ester or amide of the acid prepared using a chiral auxiliary. For example, see Evans et al., *Tetrahedron*, 44:5525 (1988), and Fadel et al., *Tetrahedron: Asymmetry*, vol. 5:4, pp. 531-534, 1994. ~~1994:531.~~

Please amend the third full paragraph appearing on page 10 as follows:

The sustained-release composition of the present invention can comprise any unit dose of active compound, generally between about 100 to 1200 mg. Preferable unit doses of 300 mg and 600 mg can be administered in a variety of combinations to obtain doses of 300, 600, 900, ~~1200 and~~ 1200, 1500, 1800, 2100, and 2400 mg. Smaller unit doses can be produced for pediatric administration, generally from about 50 to 300 mg in amount. A daily dose of drug could range between about 100 to 4800 mg, but more typically, would range between about 300 to 2400 mg.

Please amend the third full paragraph appearing on page 12 as follows:

Following oral administration, the sustained-release composition slowly releases the pharmacologically active ingredient within the body as the formulation progresses along the gastro-intestinal tract. In this regard, the gastro-intestinal tract is considered to be the abdominal portion of the alimentary canal, ~~i.e.~~ i.e., the lower end of the esophagus, the stomach and the intestines.

Please amend the third full paragraph appearing on page 14 as follows:

The matrix of the sustained-release composition also can include one or more pharmaceutically acceptable excipients recognized by those skilled in the art, ~~i.e.~~ i.e., formulation excipients. Such excipients include, for example, binders: polyvinylpyrrolidone, gelatin, starch paste, microcrystalline cellulose (such as AVICEL PH 101®, available from FMC Pharmaceutical Division, Philadelphia, PA); diluents (or fillers): starch, pregelatinized cornstarch (such as STARCH 1500®, available from Colorcon, West Point, ~~PA.),~~ PA), sucrose, dextrose, lactose, fructose, xylitol, sorbitol, sodium chloride, dextrins, calcium phosphate, calcium sulphate; and lubricants: stearic acid, magnesium stearate, calcium stearate, Precirol (mixture of mono-, di- and triesters of palmitic and stearic acid with glycerol) and flow ~~aids for example~~ aids, for example, talc or colloidal silicon dioxide. Pregelatinized cornstarch, microcrystalline cellulose, and a mixture of lactose and magnesium stearate are preferred as a formulation excipient.

Please amend the second full paragraph appearing on page 19 as follows:

In another aspect of the present invention, the sustained-release composition of the present invention comprises a semi-permeable wall surrounding the active compound, the semi-permeable wall being permeable to the passage of fluid but impermeable to the passage of ~~said~~ the active compound. The composition includes one or more exits through the semi-permeable wall for sustained release of the active compound, in accordance with the ~~method of~~ method disclosed in U.S. Patent No. 5,674,895. In such cases, the active compound can be placed inside the semi-permeable wall alone or as a sustained-release formulation such as with a matrix and/or film-coating.

Please amend the first full paragraph appearing on page 21 (and amended in the Preliminary Amendment dated September 28, 2001) as follows:

A compressed core containing the active compound and a ~~film coating~~ film coating around the core also can comprise a sugar coating containing a further dose of active drug around the ~~seal coated~~ seal-coated core as described in U.S. Patent No. 4,248,858. Sustained-release compositions of the present invention also can comprise multiple compartments as described for capsules in U.S. Patent No. 5,672,359. ~~In an~~ In a three compartment design, the outer compartment may incorporate the active compound or an odoriferous agent and excipients into a layer ~~which~~ that coats and thus surrounds the intermediate component of the capsule. This outer compartment represents the rapid or instantaneous release portion of the delivery system. The intermediate compartment comprises a powder formulation ~~which~~ that represents the intermediate rate of release portion of the delivery system. The innermost compartment incorporates the active compound in a ~~slow release~~ slow-release formulation as described above or ~~as~~ as a multiparticulate form, such as small ~~pellets~~ pellets, which may be coated or uncoated.

Please amend the paragraph bridging pages 21 and 22 as follows:

A sustained-release composition according to the invention may be formed into a solid dosage presentation according to conventional processes. The pharmacologically active compound and matrix, together with other optional pharmaceutically acceptable excipients, are mixed and then

mixed and then compressed to produce a solid formulation (Example 2). In one such ~~method~~ method, the pharmacologically active compound is mixed with a minor proportion of the matrix material of the present invention to form a dry mixture of powders. The mixture is then granulated using a binder material in a solvent such as an alcoholic ~~solvent e.g.~~ solvent, e.g., isopropyl alcohol or a mixture of a miscible organic solvent and an aqueous solvent. The wet granular mass is then dried. Other ingredients can then be added to the granules and compressed into tablets. Alternatively, if the nature of the active compound permits, all the ingredients may be dry mixed, including excipients, to form a homogeneous ~~blend~~ blend, which is then compressed to give a tablet of the correct weight.

Please amend the third full paragraph appearing on page 22 as follows:

The fluidized bed coating process involves the application of the coating material in a solution or suspension using a spray nozzle to atomize the coating solution or suspension for application to the incipient beads, which are in motion in the fluidized bed apparatus. Generally, in beads that are to be coated, the incipient beads move up a column where the coating is applied and are dried in an expansion chamber. If tablets are to be coated, the process is the same, except that no column is used. This process is cyclic in nature, occurring repeatedly until the desired amount of coating is applied. For example, see REMINGTON'S PHARMACEUTICAL SCIENCES, *supra*, and THE THEORY AND PRACTICE OF INDUSTRIAL PHARMACY, Lackman, Liberman and King, eds. (Lea and Febiger, Philadelphia, ~~1970).~~ PA, 1970).

Please amend the second full paragraph appearing on page 23 as follows:

The indicated dosage of isovaleramide and related compounds in treating CNS-effected disorders such as epilepsy or spasticity is on the order of 50 to 2400 mg per dose or 1-40 mg/kg body weight. The precise dose depends upon several factors including the nature and dose of the active compound, the particular sustained-release formulation, and the potential for inter-subject variability.

Please amend the third full paragraph appearing on page 23 as follows:

For use as an anti-convulsant, an effective concentration of isovaleramide in the serum is expected to be about 5 to 15 μg/ml with a target concentration of about 10 μg/ml. Thus, for a 70 kg patient with a plasma clearance of about 150 ml/h for isovaleramide (NPS 1776), a 1200 mg dose of isovaleramide administered twice daily (2400 mg daily dose) should achieve the target therapeutic steady state plasma concentration of about 10 μg/ml. The sustained-release formulations of the present invention provide a steady rate of drug release for at least about 8 hours and more preferably for at least about 12 hours. However, drug release rates exceeding 12 hours also are ~~contemplated~~ contemplated.

Please amend the second full paragraph appearing on page 25 as follows:

Kindling has been proposed as a model to search for drugs with antiepileptogenic efficacy (Wada, *Epilepsia*, ~~19: 217-227,~~ 19:217-227 (1974); Sato et al., *Epilepsy Res.*, ~~5: 117-124, (1990));~~ 5:117-124 (1990); Silver et al., *Ann. Neurol.*, ~~29: 356-363,~~ 29:356-363 (1991)). The term "antiepileptogenic" refers to the idea of inhibiting the processes that ~~underly~~ underlie the development of epilepsy. ~~"Anticonvulsant",~~ "Anticonvulsant," on the other hand, refers to the actual inhibition of seizures in an epileptic model.

Please amend the second full paragraph appearing on page 26 as follows:

SUBSTANCE ABUSE/CRAVING: Anticonvulsants such as carbamazepine, that have shown efficacy in kindled models of epilepsy, have also demonstrated efficacy in reducing the symptoms of affective mood disorders and substance abuse/craving in patients (Post, et al., *Ann. N.Y. Acad. Sci.*, ~~537:292-308,~~ 537:292-308 (1988); Post, et al., *Epilepsia*, ~~25:234-239,~~ 25:234-239 (1984); Post, et al., *Psychopharmacol.*, ~~72: 189-196,~~ 72:189-196 (1981); Halikas et al., *Lancet*, 8638:623-624 (1989); Blumer et al., *Compr. Psychiatry*, ~~29(2):108-22~~ 29(2):108-122 (1988)). Post et al., *Biol. Psychiatry*, 11(4):403-419 ~~(1976)~~ (1976), have demonstrated a pharmacologic (chemical) kindling model employing subconvulsive doses of cocaine as the stimulus. The progressive human response

cocaine as the stimulus. The progressive human response to high cocaine usage such as irritability, restlessness, hypervigilance, and paranoia may be a human equivalent of the kindling phenomenon observed in animals.

Please amend the paragraph bridging pages 28 and 29 as follows:

Neurogenic inflammation within the meninges has been proposed as an event in the underlying pathology of migraine headaches. Lee et al., *Brit. J. Pharmacol.*, ~~116:1661-67~~ 116:1661-1667 (1995). Compounds are tested for their ability to block the leakage of radiolabeled bovine serum albumin within the dura mater post trigeminal stimulation.

Please amend the paragraph bridging pages 29 and 30 as follows:

Kindling has been proposed as a model that can be used to identify drugs with antiepileptogenic efficacy (Wada, ~~*supra,*~~ *supra* (1974); Sato et al., ~~*suprai,*~~ *supra* (1990); and Silver et al., ~~*supra,*~~ *supra* (1991). The term "antiepileptogenic" refers to the idea of inhibiting the processes that ~~underly~~ underlie the development of epilepsy thereby providing a "neuroprotective" effect. "Anticonvulsant," on the other hand, refers to the ~~acutal~~ actual inhibition of seizures in an epileptic model. Several models of kindling are useful. The amygdala-kindled rat is such a model (Tober, *Eur. J. Pharmacol.*, ~~15:163-169,~~ 15:163-169 (1996)). Seizure kindling models are characterized by giving a sub-seizure eliciting electrical or chemical stimulus (i.e., sub-threshold) over a period of time (Goddard et al., ~~*supra,*~~ *supra* (1969)). The majority of initially non-convulsive animals that are exposed to such stimuli over a number of days, eventually exhibit seizure activity to these stimuli, have a permanently lowered threshold, exhibit altered manifestations of normal behavior and therefore are considered "kindled."

Please amend the first full paragraph appearing on page 30 as follows:

Acute cerebral insults such as status epilepticus, traumatic injury and stroke induce damage to selective neuronal populations in the hippocampus (Matsuyama et al., *J. Cereb. Blood Flow Metab.*, ~~13: 229-234, (1993));~~ 13:229-234 (1993); and Sloviter, *Science*, ~~235: 73-76, (1987))~~

~~(1987))~~ 235:73-76 (1987)), suggesting that substances designed to prevent the neuronal damage that occurs in a variety of human neurological diseases would be therapeutically useful. In Jolkkonen et al., *Neuroreport*, ~~7: 2031-2035, (1996)~~ 7:2031-2035 (1996), it was found that augmentation of GABAergic inhibition by chronic infusion of the GABA transaminase inhibitor, vigabatrin, prevented the delayed seizure-induced damage following kainate-induced status epilepticus.

Please amend the paragraph bridging pages 30 and 31 as follows:

Kindling phenomenon has been proposed to underlie the development of ~~disorders~~ disorders, such as ~~epilepsy~~ epilepsy, substance ~~abuse/craving~~ abuse/craving, and affective mood ~~disorders~~ disorders, such as bipolar (Post et al. ~~1981:~~ 1981; Post et al., 1984; Ballenger et al., 1978; Post et al., 1988). Anticonvulsants, such as ~~cambamazepine,~~ carbamazepine, that have shown efficacy in kindled models of epilepsy, have also demonstrated efficacy in reducing the symptoms of affective mood disorders and substance abuse/craving in patients (Post and Weiss, *supra* ~~(1989),~~ (1989); Halikas et al., ~~*supra,*~~ *supra* (1989); and Blumer et al., ~~*supra,*~~ *supra* (1988)). Post et al., *Biol. Psychiatry* ~~11: 403-419, (1976))~~ 11:403-419 (1976), have demonstrated a pharmacologic (chemical) kindling model employing subconvulsive doses of cocaine as the stimulus. The progressive human response to high cocaine usage such as irritability, restlessness, hypervigilance, and paranoia may be a human equivalent of the kindling phenomenon observed in animals. Recently, the anticonvulsant drug, vigabatrin, was proposed as a possible treatment for cocaine or nicotine craving (Dewey, et al., *Synapse*, ~~31:76,~~ 31:76 (1999)).

Please amend the first full paragraph appearing on page 31 as follows:

The therapeutic effects of isovaleramide, isovaleric acid, and related compounds, as illustrated in various of the assays described ~~above ,~~ above, are exploited to unexpected advantage in sustained-release formulations of the present invention. These ~~formulation~~ formulations can be used to treat the pathologies described above, including, for example, spasticity, bipolar affective disorder and convulsions/seizures. With this background, the present invention will be understood

invention will be understood more readily by reference to the following examples, which are provided for purposes of illustration and are not intended to be limiting of the invention.

Please amend the second full paragraph appearing on page 31 as follows:

Isovaleramide ~~(NPS1776)~~ (NPS 1776) was orally administered in a double-blind, placebo-controlled, ascending single dose study conducted in two groups of healthy young male Caucasian subjects and one group of healthy young female Caucasian subjects to investigate the safety, tolerability, pharmacodynamics and pharmacokinetics of the drug. Various amounts of the drug were dissolved in 250 mL of a flavored soft drink (powdered soft drink diluted in mineral water) and administered as an oral solution.

Please amend the paragraph bridging pages 33 and 34 as follows:

Sustained release was achieved with two barriers. An outside barrier is an ethyl cellulose/hydroxypropyl methyl cellulose film coat that retards diffusion of water into the tablet core and acts as a barrier against drug diffusion out from the inner core of the tablet. An inside barrier comprises xanthan gum in the tablet core matrix, which hydrates and swells to form a viscous ~~gel~~ gel.

Please amend the second full paragraph appearing on page 34 as follows:

2. Drug, xanthan gum (e.g., XANTURAL®; Monsanto, ~~St Louis, Missouri; grade NF)~~ St. Louis, MO; NF grade) and lactose (e.g. monohydrate form, spray dried,: Oread, Palo Alto, CA; NF grade) were mixed into a 1-L glass jar and blended in a Turbula mixer for four minutes at 96 rpm.

Please amend the fifth full paragraph appearing on page 34 as follows:

1. Hydroxypropyl methylcellulose (HPMC; e.g., Dow Chemical Co., Midland, ~~Michigan;~~ MI; NF grade) solution was prepared by adding ~~HMPC~~ HPMC slowly to purified water heated to approximately 80°C. The solution was allowed to cool to room temperature by placing vessel in a cold water bath. Additional water was added to prepare the final requisite amount of

amount of HPMC solution.

Please amend the Table 7 appearing on page 36 as follows:

Table 7: Formulation Composition for a 5% Film-Coated Tablet Containing 400 Mg Isovaleramide (NPS 1776)

Component	Tablet (mg)	Batch (g)	Percent (% w/w)
Isovaleramide (NPS 1776)	400.0	200.0	47.6
~~Xantham~~ Xanthan Gum	56.0	28.0	6.7
Lactose Monohydrate, Spray-dried	340.0	170.0	40.5
Magnesium ~~Stereate~~ Stearate	4.0	2.0	0.5
Core Tablet Total Weight	800.0	400.0	95.3
AQUACOAT® ECD (solids wt.)	24.4[1]	24.4[2]	2.9
Hydroxypropyl methylcellulose	9.8	9.8	1.1
Dibutyl sebacate	5.8	5.8	0.7
Purified water[3]	(63.1)	(63.1)	N/A
Coated Tablet Total Weight	**840.0**	**840.0**	**100.0**

N/A = Not Applicable,

[1] Solids content provided by 81.3 mg of suspension,

[2] Solids content provided by 81.3 g of suspension,

[3] Removed during processing.

Please amend the Table 8 bridging pages 36 and 37 as follows:

Table 8: Formulation Composition for a 12% Film-Coated Tablet Containing 400 Mg Isovaleramide (NPS 1776)

Component	Tablet (mg)	Batch (g)	Percent (% w/w)
Isovaleramide (NPS 1776)	400.0	200.0	44.6
~~Xantham~~ Xanthan Gum	56.0	28.0	6.3
Lactose Monohydrate, Spray-dried	340.0	170.0	37.9
Magnesium ~~Stereate~~ Stearate	4.0	2.0	0.4
Core Tablet Total Weight	800.0	800.0	89.2
AQUACOAT® ECD (solids wt.)	58.8[1]	58.5[2]	6.5
Hydroxypropyl methylcellulose	23.4	23.4	2.6
Dibutyl sebacate	14.1	14.1	1.6
Purified water[3]	(151.4)	(151.4)	N/A
Coated Tablet Total Weight	**896.0**	**896.0**	**100.0%**

N/A = Not Applicable,

[1] Solids content provided by 195.1 mg of suspension,

[2] Solids content provided by 195.1 g of suspension,

[3] Removed during processing.

Please amend Table 10 appearing on page 38 as follows:

Table 10: Formulation III: Composition of a 12% Film-Coated Tablet Containing 600 Mg Isovaleramide

Component	**Tablet (mg)**	**Percent (% w/w)**
Isovaleramide (NPS 1776)	600.0	66.0
Xanthan Gum	56.0	6.2
Lactose Monohydrate, Spray-dried	140.0	15.4
Magnesium Stearate	4.0	0.4
Core Tablet Total Weight	800.0	88.0
AQUACOAT® ECD (solids wt.)	48.7[1]	5.4
Hydroxypropyl methylcellulose	48.7	5.4
Dibutyl sebacate	11.7	1.2
Purified Water[2] USP	(213.6)	N/A
Coated Tablet Total Weight	**909.1 mg**	**100.0%**

N/A = Not Applicable,

[1] Solids content provided by 162.4 mg of suspension,

[2] Removed during processing.

Please amend the first full paragraph appearing on page 39 as follows:

1. Isovaleramide (NPS 1776) (200-300 gm) was mixed with microcrystalline cellulose (AVICEL PH 101®) and pregelatinized cornstarch (STARCH ~~1500®)in~~ 1500®) in a small high shear mixer. Water was added such that small agglomerates were formed.

Please amend the second full paragraph appearing on page 39 as follows:

2. The material was extruded through 1.7-mm holes with a small extruder. The extrudate was spheronized with a maurumerizer (available from Luwa, ~~Charlotte~~ Charlotte, NC) with a plate speed of 1,000 rpm. Beads were formed within 2 minutes and were tray dried in a ~~50 °C~~ 50°C oven overnight.